

Sex Disparities in Overall Burden of Disease Among HIV-Infected Individuals in the Veterans Affairs Healthcare System

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BACKGROUND: Whether sex disparities exist in overall burden of disease among human immunodeficiency virus (HIV)-infected individuals in the Veterans Affairs healthcare system (VA) is unknown.

OBJECTIVE: To determine whether sex differences exist in overall burden of disease after 1 year of combined antiretroviral therapy (ART) among HIV-infected individuals in VA.

DESIGN: Retrospective cohort study.

PARTICIPANTS: Among patients in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC), all ART-naïve HIV-infected Veterans who received VA-based HIV care between 1996 and 2009.

MAIN MEASURES: Overall burden of disease was measured using the VACS Index, an index that incorporates HIV (e.g. CD4 cell count) and non-HIV biomarkers (e.g. hemoglobin) and is highly predictive of all-cause mortality. Possible scores range from 0 to 164, although scores typically range from 0 to 50 for 80 % of patients in VACS-VC. A higher score indicates greater burden of disease (each additional five points indicates approximately 20 % increased 5-year mortality risk). ART adherence was measured using pharmacy data.

KEY RESULTS: Complete data were available for 227 women and 8,073 men. At ART initiation, compared with men, women were younger and more likely to be Black, less likely to have liver dysfunction, but more likely to have lower hemoglobin levels. Median VACS Index scores changed from ART initiation to 1 year after ART initiation: women's scores went from 41 to 28 for women (13 point improvement) and men's from 42 to 27 for men (15 point improvement). In multivariable regression, women had 3.6 point worse scores than men after 1 year on ART ($p=0.002$); this difference decreased to 3.2 points after adjusting for adherence ($p=0.004$).

CONCLUSIONS: In VA, compared to men, women experienced less improvement in overall burden of disease after 1 year of HIV treatment. Further study is needed to elucidate the modifiable factors that may explain this disparity.

KEY WORDS: women; Veterans; HIV; health care disparities; burden of illness.

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Since the introduction of combined antiretroviral treatment (ART), there has been accumulating evidence of sex disparities in HIV-related care and outcomes in the United States, with women, in general, faring worse than men.^{1–8} Prior studies have found that HIV-infected women report worse health-related quality of life⁸ and have greater HIV-related morbidity,⁵ as well as HIV-related⁶ and all-cause mortality,^{6,7} compared to HIV-infected men. These health disparities have been attributed, in part, to differences in access to care,^{1,7} quality of care,^{1–4} and ART adherence.^{9–12}

It is unknown whether similar disparities exist between HIV-infected women and men in the Veterans Affairs (VA) healthcare system. VA is the largest single provider of HIV care in the United States, providing care to over 24,000 HIV-infected Veterans annually.¹³ Within VA, women and men share similar sociodemographic characteristics, such as limited economic resources. Additionally, the potential barrier of access based on health insurance is similarly reduced for both groups.

As the number of women Veterans seeking VA care continues to increase, it is expected that the number of HIV-infected women in VA care—currently 3 % of HIV-infected persons in VA care—will also rise.^{14,15} However, there is a lack of research examining health outcomes among this unique population of women Veterans and whether sex disparities in outcomes exist among HIV-infected persons in VA care. Therefore, among HIV-infected individuals in VA care, we

sought to determine whether differences exist by sex in overall burden of disease after 1 year of ART.

METHODS

Data Source

We used data from the Veterans Aging Cohort Study Virtual Cohort (VACS-VC), a clinical cohort of 32,747 HIV-infected persons in care at VA facilities nationally.¹⁶ VACS-VC consists of data from the Clinical Case Registry, the VA's HIV registry; the Pharmacy Benefits Management database, which provides outpatient pharmacy data; and the Decision Support System, a national database of clinical data including coded diagnoses and laboratory values. We received Institutional Review Board approval for this study from VA Connecticut Healthcare System and the Yale University School of Medicine.

Study Population

Among the HIV-infected persons in the VACS-VC (821 women, 31,926 men), we included persons 1) with a date of entry to HIV care between January 1, 1996 and December 31, 2009; 2) who were confirmed to be receiving HIV care at a VA healthcare facility; and 3) who were ART-naïve, defined as having received no prior ART prescriptions while in VA care and an HIV RNA level > 500 copies/mL within 6 months prior to ART initiation. Date of entry to HIV care was defined as the earliest date of any of the following: ICD-9 code for HIV diagnosis (042 or V08) (1st inpatient or 2nd outpatient), CD4 cell count, or HIV RNA level. Patients were confirmed to be receiving HIV care if there was evidence of a CD4 cell count, HIV RNA level, or ART prescription at a VA healthcare facility.

Measures

Overall burden of disease was measured using the VACS Index, a validated index predictive of morbidity and mortality which incorporates HIV and non-HIV biomarkers.^{17,18} The VACS Index is calculated using the patient's age, CD4 cell count; HIV RNA level and hemoglobin levels; renal and hepatic function; and Hepatitis C virus serostatus (Table 1).^{17,18} Possible VACS Index scores range from 0 to 164 points with higher scores indicating greater burden of disease and higher risk of morbidity and mortality; scores range from 0 to 50 points for 80 % of patients in VACS-VC.¹⁹ A 5-point difference in VACS Index corresponds to an approximately 20 % change in 5-year mortality risk.^{19,20} Time intervals used to identify routine clinical tests for calculation of the VACS Index were consistent with prior VACS studies.¹⁹

ART adherence was measured using the medication possession ratio (MPR), a validated measure of medication adherence. MPR is the sum of the days' supply of ART in a specific period divided by the total number of days during the specified period; in this case, 365 days.^{21,22} The MPR

Table 1. Points Used to Generate Veterans Aging Cohort Study (VACS) Index Score for Overall Burden of Disease

Component	VACS Index
Age years	
< 50	0
50 to 64	12
≥ 65	27
CD4 cells/mm ³	
≥ 500	0
350 to 499	6
200 to 349	6
100 to 199	10
50 to 99	28
< 50	29
HIV RNA copies/mL	
< 500	0
500 to 1 × 10 ⁵	7
> 1 × 10 ⁵	14
Hemoglobin g/dL	
≥ 14	0
12 to 13.9	10
10 to 11.9	22
< 10	38
FIB-4	
< 1.45	0
1.45 to 3.25	6
> 3.25	25
eGFR mL/min	
≥ 60	0
45 to 59.9	6
30 to 44.9	8
< 30	26
Hepatitis C	5

FIB-4: Fibrosis Index = (years of age × aspartate transaminase) / (platelets in 10⁹/L × square root of alanine transaminase)

eGFR: estimated Glomerular Filtration Rate = 186.3 × (serum creatinine^{-1.154}) × (age^{-0.203}) × (0.742 for women) × (1.21 if black)

was dichotomized as < 80 % (poor adherence) vs. ≥ 80 % (high adherence).²³

Statistical Analysis

We used chi-square and Wilcoxon-rank sum tests to compare VACS Index components and total VACS Index scores by sex at ART initiation and after 1 year on ART. We assessed the association between sex and our outcome of interest, VACS Index score after 1 year on ART, with and without adjustment for VACS Index score at ART initiation, age, and poor ART adherence using linear regression. VACS Index score at ART initiation was centered at the median (42), so that the intercept for models adjusted for score at ART initiation represents those with the median value rather than zero. Age, modeled in 5-year increments, was centered at 47, such that the intercept, in models adjusted for age, represents the 1-year score for a 47-year-old patient. We used age at ART initiation when calculating all VACS Index scores to avoid increasing scores due to the increase in age by 1 year. We included age in multivariate models, because women in our cohort were younger and we wanted to adjust for this potential confounder. Associations with VACS Index score at 1 year after ART initiation are presented as betas (β) with associated 95 % confidence intervals (CI) and *p* values. Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Of 275 women and 9,809 men who met study criteria, complete data were available for 227 women (82.5 %) and 8,073 men (82.3 %) at both ART initiation and 1 year after. At ART initiation, women were younger (42 [IQR 37–48] vs. 47 [IQR 40–53] years, $p<0.001$) and more likely to be Black (69.2 % vs. 55.1 %, $p<0.001$) (Table 2). Women were less likely to have liver dysfunction (33 % vs. 48 %, $p<0.001$), but more likely to have lower hemoglobin levels (12.0 vs. 13.4 [IQR 12.0–14.6] g/dL, $p<0.001$). There were no statistically significant differences by sex with respect to CD4 cell count (237 [IQR 100–363] vs. 230 [IQR 68–341] cells/mm³, $p=0.07$), HIV RNA levels, renal function, Hepatitis C infection, or VACS Index score.

Association Between Patient Sex and Overall Burden of Disease 1 Year After ART Initiation

VACS Index scores, our measure of overall burden of disease, changed for both groups over 1 year of ART (Fig. 1). Baseline to 1 year scores changed from: 41 to 28 for women (13 point improvement), equivalent to a decrease of 8.8 % in 5-year mortality risk; and 42 to 27 for men (15 point improvement), a decrease of 10.2 % in 5-

year mortality risk. Because the translation of a difference in VACS Index score to an expected mortality rate depends upon baseline score, one must interpret these changes in this context.

In unadjusted analysis, patient sex was not associated with VACS Index score 1 year after ART initiation (β , +1.3, 95 % CI, -1.7 to 4.3) (Table 3). However, VACS Index score at ART initiation, age, and poor ART adherence were each significantly associated with score at 1 year after ART initiation. In multivariable analysis, women's scores were 3.6 points higher (i.e. greater overall burden of disease) than men ($p=0.002$). Thus, adjusted differences in VACS Index score were even greater than in our unadjusted analyses. After further, adjustment for ART adherence, women's scores remained 3.2 points higher than men ($p=0.004$).

DISCUSSION

HIV-infected women in the VA Healthcare system experience less improvement in overall burden of disease after 1 year of ART compared to HIV-infected men, a difference

Table 2. Characteristics of Combined Antiretroviral Therapy (ART)-Naïve HIV-Infected Women and Men in VA Care at ART Initiation and 1 Year After ART Initiation

		ART initiation			One year after ART initiation		
		Women (n=227) N (%)	Men (n=8,073) N (%)	<i>p</i>	Women (n=227) N (%)	Men (n=8073) N (%)	<i>p</i>
Age years	< 50	190 (83.7)	4981 (61.7)	< 0.001			
	50 to 64	37 (16.3)	2746 (34.0)				
	≥ 65	0 (0.0)	346 (4.3)				
Race/ethnicity	White	60 (26.4)	2794 (34.6)	< 0.001			
	Black	157 (69.2)	4446 (55.1)				
	Hispanic	8 (3.5)	563 (7.0)				
	Other/Unknown	2 (0.9)	270 (3.3)				
CD4 cells/mm ³	≥ 500	24 (10.6)	809 (10.0)	0.34	61 (26.9)	1837 (22.8)	0.60
	350 to 499	38 (16.7)	1106 (13.7)		50 (22.0)	1640 (20.3)	
	200 to 349	70 (30.8)	2228 (27.6)		53 (23.3)	2101 (26.0)	
	100 to 199	39 (17.3)	1455 (18.0)		34 (15.0)	1413 (17.5)	
	50 to 99	15 (6.6)	796 (9.9)		12 (5.3)	494 (6.1)	
HIV RNA copies/mL	< 50	41 (18.1)	1679 (20.8)	0.24	17 (7.5)	588 (7.3)	0.63
	< 500	0 (0)	0 (0)		130 (57.2)	4875 (60.4)	
	500 to 1 × 10 ⁵	152 (67.0)	5097 (63.1)		78 (34.4)	2594 (32.1)	
	≥ 1 × 10 ⁵	75 (33.0)	2976 (36.9)		19 (8.4)	604 (7.5)	
Hemoglobin g/dL	≥ 14	26 (11.5)	3049 (37.8)	< 0.001	38 (16.7)	4038 (50.0)	< 0.001
	12 to 13.9	93 (41.0)	3017 (37.4)		110 (48.5)	3006 (37.2)	
	10 to 11.9	78 (34.4)	1437 (17.8)		59 (26.0)	798 (9.9)	
	< 10	30 (13.2)	570 (7.1)		20 (8.8)	231 (2.9)	
FIB-4	< 1.45	152 (67.0)	4192 (51.9)	< 0.001	174 (76.7)	4945 (61.3)	< 0.001
	1.45 to 3.25	54 (23.8)	2942 (36.4)		41 (18.1)	2456 (30.4)	
	> 3.25	21 (9.3)	939 (11.6)		12 (5.3)	672 (8.3)	
eGFR mL/min	≥ 60	217 (95.6)	7541 (93.4)	0.58	215 (94.7)	7391 (91.6)	0.35
	45 to 59.9	6 (2.6)	281 (3.5)		8 (3.5)	380 (4.7)	
	30 to 44.9	2 (0.9)	102 (1.3)		2 (0.9)	127 (1.6)	
	< 30	2 (0.9)	149 (1.8)		2 (0.9)	175 (2.2)	
Hepatitis C VACS Index		69 (30.4)	2971 (36.8)	0.05			
	0 to 34	86 (37.9)	3159 (39.1)	0.44	139 (61.2)	5221 (64.7)	0.01
	35 to 49	57 (25.1)	1677 (20.8)		55 (24.2)	1338 (16.6)	
	50 to 69	47 (20.7)	1760 (21.8)		18 (7.9)	965 (12.0)	
	70+	37 (16.3)	1477 (18.3)		15 (6.6)	549 (6.8)	

IQR interquartile range; FIB-4 Fibrosis Index; eGFR estimated Glomerular Filtration Rate

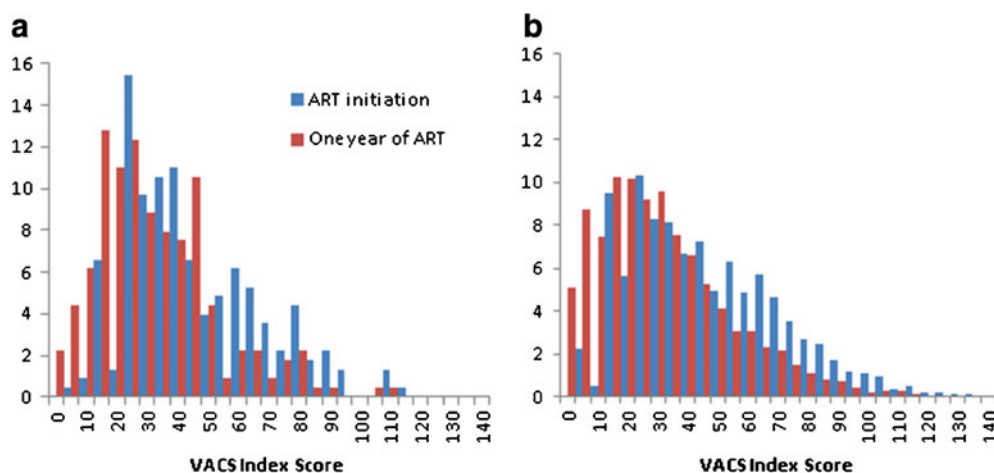


Figure 1. Veterans Aging Cohort Study (VACS) index scores at combined antiretroviral therapy (ART) initiation and one year after ART initiation. **a** VACS Index score, women; **b** VACS Index score, men.

only modestly explained by ART adherence. This study, which utilized a large clinical cohort of HIV-infected Veterans in VA-based HIV care, represents the first comprehensive analysis of health outcomes for HIV-infected women Veterans in VA care.

Our findings contribute to characterizing and understanding health outcomes for HIV-infected women in VA care. By using the VACS Index, a measure of overall burden of disease that includes both HIV and non-HIV biomarkers, we were able to go beyond what traditional measures (e.g. CD4 cell count) tell us about morbidity to capture a more global assessment of health among HIV-infected women Veterans, including their response to treatment. This is particularly important, given the increased contribution of non-AIDS defining disease to morbidity and mortality in the ART era and the complex interplay of HIV infection, ART and comorbid disease in an aging HIV population. In validation studies of the VACS Index, we also looked at whether hemoglobin level behaved differently between women and men in its contribution to VACS Index score and its association with mortality, and found no evidence that it did.¹⁹ Further, VACS Index predicted mortality rates matched observed rates as well for men as for

women.²⁰ Results from prior studies of HIV-related sex disparities using traditional HIV biomarkers have been mixed with respect to whether or not sex differences exist in response to ART;^{24–27} however, larger studies have found no sex differences in ART response.^{28–31} How findings from these studies would have differed if overall burden of disease were assessed is unknown. Additionally, our study findings suggest that differences in ART adherence only minimally contribute to this disparity in ART response.

Our study has several limitations. First, to calculate the VACS Index requires data on eight routine clinical tests. However, we had complete data for over 80 % of individuals in our study sample at the two clinical time points. Second, since the study's focus was on the VA population, our results may not be generalizable to HIV-infected persons who receive care outside the VA healthcare system, as the VA HIV population is older than the general HIV population. It is also affected by a substantial burden of chronic comorbid disease,^{32,33} which has been increasingly ascribed to HIV-associated chronic inflammation as well as ART-associated toxicity.^{18,34–36} Additionally, HIV-infected women Veterans

Table 3. Association Between Patient Sex and Veterans Aging Cohort Study (VACS) Index Score at 1 Year After Combined Antiretroviral Therapy (ART) Initiation

	Unadjusted			Model 1*			Model 2†		
	β	(95 % CI)	P	β	(95 % CI)	p	β	(95 % CI)	P
Intercept	30.2	(29.8, 30.7)		28.6	(28.3, 29.0)		24.3	(23.8, 24.8)	
Women vs. Men	1.3	(−1.7, 4.3)	0.39	3.6	(1.3, 5.9)	0.002	3.2	(1.0, 5.4)	0.004
VACS Index score at ART initiation, points	0.5	(0.5, 0.6)	< 0.001	0.5	(0.5, 0.5)	< 0.001	0.5	(0.5, 0.5)	< 0.001
Age, 5-year increment	4.7	(4.4, 4.9)	< 0.001	2.2	(2.0, 2.5)	< 0.001	2.4	(2.2, 2.6)	< 0.001
Adherence < 80 %	7.7	(6.7, 8.6)	< 0.001				8.9	(8.2, 9.7)	< 0.001

SE standard error

*Model 1 indicates adjusted for VACS Index score at ART initiation and age

†Model 2 indicates adjusted for VACS Index score at ART initiation, age, and poor ART adherence

Intercept represents men in unadjusted regression analysis; men, age 47 with VACS Index score of 42 at ART initiation in Model 1; and men, age 47, with VACS Index score of 42 at ART initiation and adherence ≥ 80 % in Model 2

may differ from HIV-infected women who are not Veterans with respect to certain sociodemographic characteristics and potential barriers to care, such as a history of military sexual trauma.³⁷ Third, by using data in the medical record, we are limited in our ability to qualitatively explore the experiences of HIV-infected women Veterans in VA care and the various barriers they may face that affect their interactions with VA healthcare system. These experiences could be further assessed in the future using the VACS prospective cohort, in which patients complete annual questionnaires.³³

We believe our findings have important implications for the care of HIV-infected women Veterans and for future research aimed at improving their health outcomes. Further study is needed to elucidate modifiable factors that may explain the observed sex disparity in ART response, such as ART-associated toxicity. Prior research suggests that women experience more and different types of ART-related adverse events and toxicity compared with men;^{38–40} this difference may affect health outcomes not only due to increased discontinuation of ART, but to direct toxic effects of ART. Also, the use of non-HIV biomarkers in addition to traditional HIV biomarkers in assessing overall burden of disease among HIV-infected persons in care provides a more comprehensive evaluation of health; potential differences between groups, such as HIV-infected women and men in VA care, may not be apparent when only traditional HIV biomarkers are considered. This suggests that broader use of measures, such as the VACS Index, in clinical care and research would be useful. Future studies of this disparity in ART response will need to explore the role of psychosocial and structural factors that differentially impact women Veterans, such as military sexual trauma, as well as whether sex differences in ART response persist over longer periods of follow-up.

In this study of HIV-infected Veterans in VA care, women had less improvement in overall burden of disease after 1 year on ART compared with men. As HIV-infected women Veterans represent a vulnerable group within a population already at high risk for poor health outcomes, it is particularly important that the root causes of this observed disparity be identified and appropriately addressed.

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